COVID-19 Sequelae Affecting Ear, Nose and Throat

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10.1 Introduction

Otorhinolaryngologic (ENT) manifestations have been recognized as salient features of SARS-CoV-2 infection since the beginning of the COVID-19 pandemic [1]. These symptoms from the upper aerodigestive tract were predominant in the subset of COVID-19 patients presenting with mild to moderate symptomatology [2]. In a large study performed on 225 patients affected with mild COVID-19 from a tertiary care center in India, at least 1 ENT symptom was identified in 62.2% of the study population [2]. The most commonly reported symptom was odynophagia (63.5%) followed by smell and taste disturbances (20% overall and 46.8% of ENT manifestations). These results were comparable with the outcomes reported in a recently concluded systematic review and meta-analysis [3].

As the pandemic evolved, it was observed that certain ENT manifestations persisted even after a patient was deemed to have been cured of COVID-19 [4, 5]. These manifestations, therefore, fall under the spectrum of post-COVID-19 sequelae, if duration of symptoms persists beyond 12 weeks from the diagnosis of COVID-19 [6]. Certain upper aerodigestive tract symptoms also emerged in patients following COVID-19 recovery that could be attributed to therapeutic interventions directed toward COVID-19 or immunological origin secondary to COVID-19 rather than a true manifestation of post-COVID-19 sequelae [7–9]. Figure 10.1 depicts the wide array of ENT manifestations reported in literature persisting beyond the diagnosis of COVID-19. This chapter will discuss the ENT manifestations in light of post-COVID-19 sequelae emphasizing pathophysiology and evidence-based management.

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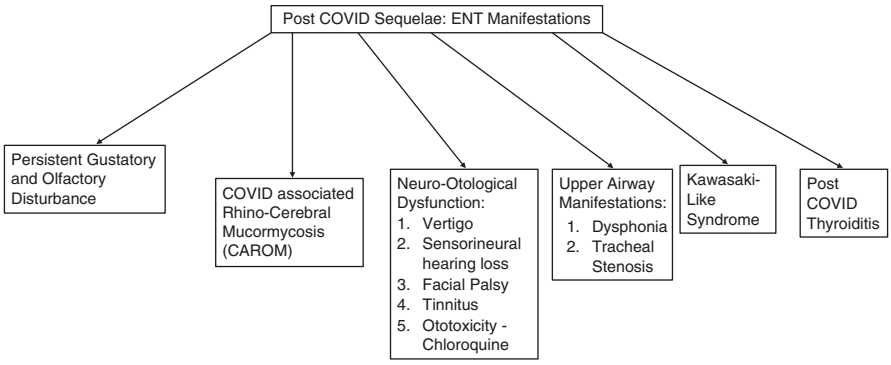

Fig. 10.1 Spectrum of ENT manifestations described in association with post-COVID-19 sequelae

10.2 Smell and Taste Disturbances

10.2.1 Epidemiology

Gustatory and olfactory disturbances have long been recognized as sequelae of viral illness. The viruses implicated include rhinovirus, parainfluenza virus, and Epstein-Barr virus [10, 11]. Anosmia (complete loss of smell) has a reported incidence of 1% globally [12]. Of these, post-infectious olfactory dysfunction (PIOD) accounts for 11% of the cases and 20–30% in high-volume referral centers [12–14]. COVID-19 as a contributor to PIOD revealed some interesting characteristics. Various degrees of smell and taste disturbances have been reported during the course of the illness. In a large multicentric European study involving patients with mild to moderate symptomatology, smell and taste disturbances were reported in 85.6% and 88%, respectively [15]. A systematic review and meta-analysis investigating possible ethnic differences in the smell and taste disturbances revealed a pooled incidence rate of 47.4% for combined olfactory and taste disturbance [16]. This study identified lower incidence rates in studies reported from Asia (17.7%) compared to Europe (54.8%). Apart from contributing to chemosensory loss in a large proportion of individuals, olfactory and gustatory disturbances were noted to be the sentinel symptom in 25% of patients in the study performed by Kaye et al. using the "Anosmia Reporting Tool" [17]. Studies using patient-reported outcomes and questionnaires reported lower incidence rates than studies utilizing objective smell identification tools as the former was prone to recall bias [16]. Given the disease burden of COVID-19 infectivity and the preponderance of chemosensory dysfunction in infected individuals, an estimated incidence of 20 million individuals has been drawn to have perceived some degree of chemosensory dysfunction [18].

10.2.2 Natural History of COVID-19 Chemosensory Dysfunction

In the multicentric European study, the overall early recovery rate was to the tune of 44% [15]. Of all affected persons, 72.6% recovered their smell and taste disturbance within 8 days. In the study conducted on mild COVID-19 patients from India, 96% of patients had recovered completely at 4 weeks [2]. These studies reflect the overall reversibility and excellent prognosis of COVID-19 chemosensory dysfunction. There is a lack of evidence about the true incidence of long-standing PIOD following COVID-19. Vaira and colleagues prospectively evaluated 138 patients diagnosed with COVID-19 to elucidate long-term recovery rates of chemosensory dysfunction [19]. They found that 7.2% of patients had persistent severe PIOD 60 days from the day of diagnosis of COVID-19. Continued dysfunction for smell at 20 days and continued taste dysfunction at 10 days were risk factors for persistent PIOD. This provided an insight into the possibility of initiating therapeutic strategies during this critical window period.

10.2.3 Reinfection Anosmia

Lechien et al. have reported two cases of chemosensory dysfunction occurring in the reinfection to COVID-19 setting in individuals who had previously experienced similar dysfunction and had fully recovered from it [20].

Favorable indicators toward the recovery of long-standing chemosensory dysfunction include the following:

(a) The appearance of parosmia [21].
(b) Olfactory bulb (OB) volume determined on coronal T2-weighted MRI revealing a volume of 40 cc for one olfactory bulb is generally indicative of recovery [22].

10.2.4 Pathophysiology

1. *Obstruction of nasal airflow*: This theory is the most frequent explanation for non-COVID-19 PIOD, especially during the acute phase of viral infection [10]. Viruses causing upper respiratory tract infection typically induce inflammation and edema of the nasal mucosa resulting in obstruction to transport of odorants to the olfactory epithelium. This variety of PIOD reverses as and when inflammation subsides. This mechanism is unlikely to be the basis for the widely reported COVID-19-induced PIOD because symptoms of nasal mucosal inflammation are infrequent in COVID-19 [23].
2. *Virus-induced destruction of olfactory neuron and epithelium*: This theory again explains PIOD in the non-COVID-19 settings, especially those cases where

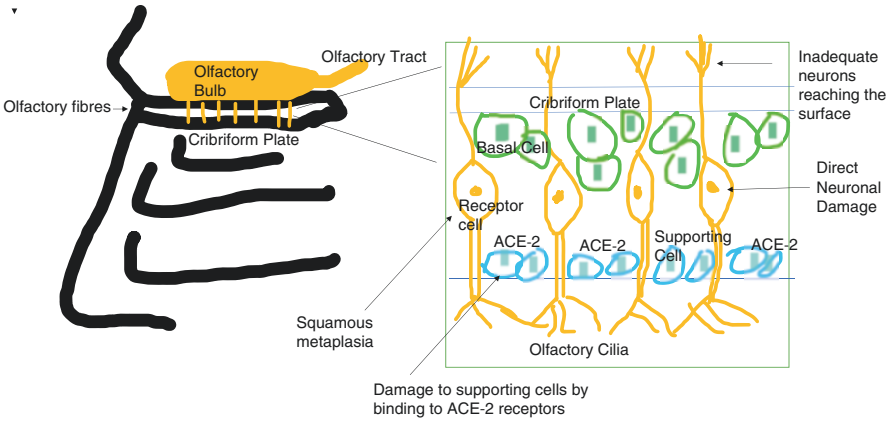

Fig. 10.2 Schematic representation of mechanism behind virus-induced chemosensory disturbance

there is permanent chemosensory dysfunction (Fig. 10.2). Histopathological studies and animal models have provided great insight into the pathophysiology of virus-induced PIOD:

(a) There is ultrastructural evidence of direct neuronal injury induced by a viral infection, in the form of partial loss of neurons, disorganized epithelium with reduced olfactory receptor cells, nerve bundles, and squamous metaplasia [24].

(b) There is inadequate number of neurons that reach the epithelial surface, thereby not coming in contact with the odor stimulant [25].

(c) In a mouse model of COVID-19, extensive damage of olfactory epithelium was identified by Bryche et al. This resulted in the exposure of olfactory neurons. The virus could be isolated from the epithelium at day 2 and the viral load gradually reduced till day 4. However, the virus could not be demonstrated in the olfactory bulb or cortex [26].

Though this theory holds for non-COVID-19 PIOD, its relevance in COVID-19-induced PIOD is questionable. This is due to the absence of ACE-2 and TMPRSS2 receptors in olfactory neurons. The presence of these receptors serves as portals for the entry of SARS-CoV-2 [27].

3. *Virus-induced damage of sustentacular cells in the olfactory epithelium*:
Unlike olfactory neurons, the sustentacular cells in the olfactory epithelium harbor ACE-2 and TMPRSS2 receptors. Bilinska et al. have proposed the mechanism for COVID-19-induced PIOD resulting from virus-induced destruction of sustentacular cells [27].

10.2.5 Diagnostic Work-Up

Detailed evaluation protocol is available in Table 10.1.

Table 10.1 Suggested work-up for post-infectious olfactory disturbance

Work-up strategy	Description
History	• Detailed history: onset, duration; specifics of impairment, qualitative or quantitative, accompanying gustatory impairment, effect on quality of life • Identify red flags: neurological symptoms, unilateral nasal obstruction, persistent headache, weight loss
ENT examination	• Endoscopic evaluation: rigid or flexible endoscope • Visualize olfactory cleft • Identify inflammatory conditions • Identify space-occupying lesions obstructing airflow toward olfactory cleft
Imaging	• NCCT PNS: opacification of olfactory cleft. Rule out inflammatory and neoplastic conditions • MRI brain and PNS: T2-weighted sequence to evaluate olfactory bulb area (volume, sulcus depth). Volumetric assessment of olfactory eloquent areas
Olfactory testing	
Subjective patient-reported outcomes	• Examples: visual analogue scale, questionnaire for olfactory dysfunction • To be used in conjunction with objective testing • Ideal for monitoring response to intervention
Psychophysical testing	Components of olfactory testing: • Odor threshold: lowest concentration of the odorant perceived by the patient. Does not require odor identification • Odor discrimination: ability to differentiate between the odors • Odor identification: ability to correctly name the odorant being presented Commercially available kits: • Sniffin' Sticks test • Smell diskettes • UPSIT (University of Pennsylvania Smell Identification Test) • Connecticut Chemosensory Clinical Research Centre Test • Toyota and Takagi olfactometer • U-Sniff • European retronasal test
Objective functional testing	• Olfactory event-related potentials • Functional MRI

Essential components of diagnostic work-up include [18]:

- *Nasal endoscopy*: Conductive pathologies impairing nasal airflow in the region of the olfactory cleft need to be ruled out before diagnosing PIOD.
- *Subjective patient-reported questionnaires*: Table 10.1 enumerates the various validated structured patient-reported questionnaires available for olfactory and gustatory function evaluation.
- *Psychophysical testing*: This involves presenting an olfactory stimulant and recording the patient's outcome. A detailed description of psychophysical testing is provided in Table 10.1. The integral components include:

  - Odor threshold
  - Odor discrimination
  - Odor identification
- *Electrophysiology*: This involves presenting odor stimuli and recording event potentials from recording electrodes placed in the olfactory epithelium (electro-olfactogram).
- *Imaging*: T2-weighted coronal MRI of the paranasal sinus and brain should be performed to evaluate the following parameters:
  - Olfactory bulb volume
  - Olfactory sulcus depth
  - Volumetric assessment of olfactory eloquent regions of the brain
  - To identify pathologies interfering with airflow to the olfactory cleft: polyp, septal deviation, space-occupying lesions, chronic rhinosinusitis, and turbinate hypertrophy

In non-contrast CT of paranasal sinuses, opacification of olfactory cleft also correlates well with olfactory disturbance post-COVID-19 [28].

Functional MRI: This modality provides a dynamic assessment of olfaction-associated cortical activity. fMRI facility is not easily available, and hence, the use of this modality should be restricted to clinical trials and research purposes.

10.2.6 Management

Table 10.2 summarizes the various therapeutic interventions reported in the literature for COVID-19-induced chemosensory dysfunction.

The Cochrane Library has initiated a live systematic review and meta-analysis to identify randomized trials for the prevention of COVID-19-induced prolonged PIOD [29] and has identified only one randomized controlled trial. Abdelalim et al. randomized patients with less than 4 weeks of olfactory disturbance to receive either topical nasal corticosteroids (mometasone furoate) or no treatment (both groups received additional olfactory training) [30]. No statistically significant difference was noted between the two groups on serial follow-up. The authors concluded the lack of superiority of topical steroid therapy over and above olfactory training.

10.2.7 Olfactory Training

Olfactory training involves regular presentation of standardized formulation of olfactory stimulants to the participants, who in turn are encouraged to focus on the memory of the odor being presented. Presumed mechanisms of action include reorganization of the olfactory epithelium, olfactory bulb, and neural olfactory pathway [29].

Table 10.2 Summary of potential therapeutic options for COVID-19-induced PIOD

Treatment strategy	Salient features
Conservative management	• One-third of patients with PIOD recover spontaneously Rate of recovery: degree of initial loss, patient age, and duration of loss
Smoking cessation	Degree of olfactory dysfunction is greater with ongoing smoking. Therefore, smoking cessation should be encouraged
Olfactory training	Robust evidence available favoring olfactory training strategies in recovery of PIOD
Corticosteroids	• Poor quality of evidence in non-COVID-19 PIOD • No consensus on oral versus intranasal steroid, dose, and frequency of administration Paucity of evidence in COVID-19-associated PIOD. Individualized risk-benefit assessment should be taken into consideration prior to initiating oral steroids • Intranasal steroid administered by Kaiteki technique improves bioavailability at the level of olfactory cleft
Theophylline	• Inhibit phosphodiesterase and increase cyclic AMP • Assists in neuroepithelium regeneration • Existing evidence insufficient to guide its use in PIOD
Sodium citrate	• Intranasal route • Ability to sequester calcium ions, reducing free mucosal calcium, inhibiting negative feedback loop, and increasing sensitivity to odorant • Mixed results in its efficacy in non-COVID-19 PIOD
N-methyl-D-aspartate antagonist	• Caroverine • Inhibiting olfactory bulb feedback mechanism • Requires well-designed RCT to determine efficacy in COVID-19 PIOD
Alpha lipoic acid	• Stimulates expression of nerve growth factors: substance P, neuropeptide Y • Neuroprotective effect • Moderate improvement in olfaction in non-COVID-19 PIOD
Vitamin A	• Regeneration of neuroepithelium • Studies have explored systemic as well as intranasal vitamin A
Minocycline	• Anti-apoptotic agent • No proven benefit in PIOD
Zinc sulfate	No available evidence favoring the use of zinc sulfate in improving olfactory function in PIOD

1. Classic Olfactory Training: This therapy involves 5-min exposure of four odorants twice a day: phenyl ethyl alcohol, eucalyptol, citronella, and eugenol. The duration of therapy is for 12 weeks.
2. Modified Olfactory Training: This variant of olfactory training is divided into three parts, each consisting of 12 weeks of therapy as described above:
   12 weeks: Twice a day 5-min exposure of phenyl ethyl alcohol, eucalyptol, citronella, and eugenol
   12 weeks: The above regime is followed by another 2 weeks of therapy with 5 min twice a day exposure of menthol, thyme, tangerine, and jasmine.

12 weeks: The last 12 weeks comprise exposure to green tea, bergamot, rosemary, and gardenia

Pekala et al. and Sorokowska et al. have independently demonstrated the benefit of the above intervention in the pre-COVID-19 era by their systematic review and meta-analysis [31, 32].

10.2.8 Role of Steroids

In a recently concluded review, significant heterogeneity was noted in studies evaluating the role of steroids in PIOD in terms of formulation, route of administration, and dosage [18]. The action of steroids in PIOD is mainly in reducing the inflammatory component of olfactory dysfunction rather than any beneficial effect on the olfactory neuroepithelium [18]. At present, there is no clarity whether oral or topical formulation should be preferred in the case of post-COVID-19 PIOD. The other issue plaguing the studies conducted on the role of steroids in COVID-19 PIOD is the confounding factor of rampant steroid administration in cases of moderate to severe COVID-19 as well as in post-COVID-19 sequelae. Currently, there is no robust indicator to administer oral corticosteroids for chemosensory dysfunction following COVID-19. Many studies have revealed the promising role of topical steroids, provided they are administered accurately to deliver the drug to the olfactory cleft [33, 34]. Kaiteki position has been advocated for improving the bioavailability of topical steroids at the level of the olfactory cleft [35]. This involves lying down on one side with the extension of the chin and neck in an upward direction. Kaiteki position increases steroid availability to olfactory cleft by 96% in the decongested nose and 75% in the non-decongested nose [35].

10.3 Phantosmia

Phantosmia or olfactory hallucination has been described in the background of COVID-19. Compared to the chemosensory dysfunction described above, reports of phantosmia are restricted to anecdotal reports [36].

10.4 COVID-19-Associated Rhino-Orbito-Cerebral Mucormycosis (CAROM)

10.4.1 Etiopathogenesis

The causative agent behind the pathogenesis of acute invasive fungal sinusitis belongs to the order Mucorales, followed by *Aspergillus* species. The species most commonly isolated is *Rhizopus oryzae*. The other less commonly reported species include *Mucor*, *Absidia*, and *Cunninghamella* [37]. These fungal pathogens are

ubiquitous in the environment and result in fulminant sinusitis in a susceptible host in the presence of suitable environmental conditions favoring its growth (tropical climate and high humidity) [38]. The host factors responsible for the development of acute invasive mucormycosis are as follows [39]:

- Uncontrolled diabetes mellitus
- Steroid use
- Post-organ transplant immunosuppression
- Retroviral disease
- Hematological malignancy
- Malnutrition
- Severe burns
- Long-term chemotherapy

The hallmark clinical features of acute invasive rhino-orbito-cerebral mucormycosis (ROCM) have been described by Smith and Kirchner et al. in 1950 [40] (Fig. 10.3):

- Black, necrotic turbinate associated with nasal crusting and blood-tinged nasal discharge
- Characteristic facial pain with or without paresthesia along the second division of trigeminal nerve (early sign)
- Periorbital or peri-nasal swelling with or without discoloration or blackening
- Orbital symptoms: ptosis, proptosis, vision loss, and complete ophthalmoplegia
- Multiple cranial neuropathies—rapid onset. Cranial neuropathy may be unrelated to the clinically apparent disease extension

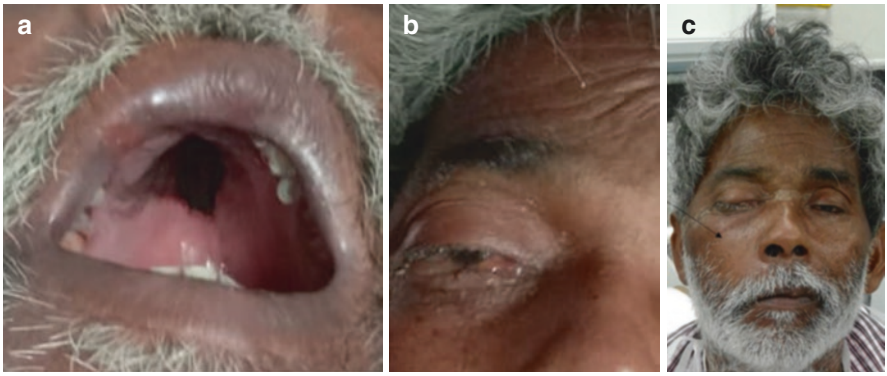

Fig. 10.3 Clinical features of CAROM. (**a**) Black eschar formation over the palate. (**b**) Complete ophthalmoplegia, vision loss, and chemosis signifying cavernous sinus involvement. (**c**) Disease extension to premaxillary soft tissue presenting as cheek fullness (arrow)

The constellation of symptoms described above in the background of a susceptible host should prompt the clinician to consider the possibility of ROCM.

ROCM most commonly presents with sinonasal involvement (88.9%) followed by orbital and cavernous sinus extension (56.7%) and intracranial involvement (22.2%) [41]. Talmi et al. have proposed a staging system for ROCM with discriminative power in terms of survival outcome [42]:

- Stage I—disease localized to the nose only with minimal soft tissue invasion (100% survival)
- Stage II—disease limited to the nose, ipsilateral sinus, and orbit (80% survival)
- Stage III—disease extending to intracranial structures with unimpaired or minimal impairment of cognition (67% survival)
- Stage IV—disease involving intracranial structures with impaired consciousness or hemiplegia, bilateral disease, skin necrosis, and palatal involvement (0% survival)

10.4.2 ROCM in the Background of COVID-19: CAROM

The second wave of the COVID-19 pandemic in India witnessed a dramatic surge in the incidence of ROCM. The pre-pandemic incidence of ROCM has been 0.14/1000 population which is 80 times higher than the incidence quoted from western literature [43]. However, the second wave-associated ROCM resulted in 14,872 cases being reported as of May 28, 2021 [44]. The salient features of CAROM are summarized as follows:

- CAROM has been described as both synchronous with the detection of COVID-19 and after recovery from the viral illness. On an average, CAROM developed 17.6 days following the onset of COVID-19. This time period was longer, with cases being reported 4–5 weeks from the onset of COVID-19 toward the beginning of the CAROM wave [45].
- The predominant comorbid condition associated with CAROM was uncontrolled diabetes mellitus, with few studies quoting 100% association. About 70% of the patients had a documented blood glucose level greater than 300 mg/dl at presentation [46]. A systematic review reported a pooled incidence of concomitant ketoacidosis to be 14.9% [41].
- The same systematic review identified steroid usage in 76.3% CAROM cases [41]. Nevertheless, CAROM was predominantly reported in patients with mild to moderate disease rather than severe COVID-19 illness [47]. According to the report from AIIMS, New Delhi, CAROM was associated with mild COVID-19 in 54%, moderate disease in 33%, and severe disease in 13%, respectively [48].
- CAROM is a fulminant disease with time to initiation of treatment having a direct bearing on survival outcomes. Time-sensitive initiation of surgical debridement and antifungal therapy can have a tremendous impact on prognosis. The

mortality rate of CAROM ranges from 33 to 80%. A delay of 6 days in the initiation of treatment can double the incidence of 30-day mortality [49].
- Survival is found to be higher in patients who undergo complete surgical debridement along with timely initiation of antifungal treatment (64.9%) versus patients who only receive antifungal treatment (21.73%) [7].

10.4.3 Pathogenesis of CAROM

Figure 10.4 depicts the complex interplay of various factors unique to COVID-19 that predisposes an individual to CAROM:

- *Role of ACE-2 receptors*: Since there is generalized upregulation of ACE-2 receptors in COVID-19, the upregulation in pancreatic islet cells causes insulin resistance [50].
- *Concomitant uncontrolled diabetes mellitus*: Hyperglycemia and the acidic pH associated with the development of ketoacidosis in the background of COVID-19-induced hypoxia provide an ideal substrate for the growth of mucormycosis. Hyperglycemia upregulates the expression of glucose-regulator protein 78 (GRP-78) of endothelium cells and fungal ligand spore coating homolog (CotH) protein. This facilitates angioinvasion, hematogenous dissemination, and tissue necrosis [41, 51].
- *Neutrophil and T cell dysfunction*: COVID-19 infection dysregulates the balance between CD-4 and CD-8 T cells and reduces CD-4 lymphocyte-induced gamma

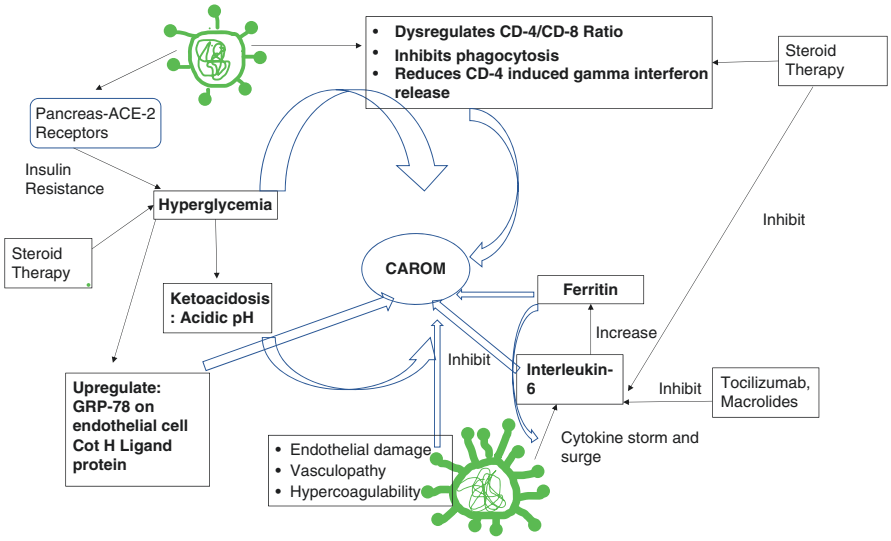

Fig. 10.4 Pathogenesis of CAROM

interferon release, thereby blunting phagocytic response against opportunistic bacterial and fungal infection [52].

- *Role of steroid therapy*: The role of steroid therapy has been widely investigated. Glucocorticoids are known to give rise to a hyperglycemic state. Glucocorticoids also interfere with phagocytic function by inhibiting pro-inflammatory cytokines like IL-6 and inhibiting phagocytosis [47].
- *Role of IL-6*: Interleukin-6 plays the role of a double-edged sword. COVID-19, a pro-inflammatory state, is associated with a surge of IL-6 levels (cytokine storm). IL-6, in turn, interferes with iron metabolism by increasing ferritin levels. Very high ferritin levels perpetuate the pro-inflammatory cascade and provide excellent conditions for mucormycosis to thrive and perpetuate the disease process. High ferritin levels also induce iron-free radical-induced oxidative damage [53]. However, IL-6 is known to mount an immune response against opportunistic infection. Use of steroid and IL-6 inhibitor tocilizumab interferes with IL-6-induced phagocytic property, thereby predisposing to opportunistic fungal infection [54]. Macrolide antibiotics like azithromycin, which were frequently administered to COVID-19 patients, are also known to inhibit IL-6 production [55].
- *Role of serum ferritin*: Increased ferritin levels seen in COVID-19 infection owing to a pro-inflammatory state predispose to the development of ROCM as Mucorales thrive in an environment rich in iron [41].
- *Hypercoagulopathy and vasculitis*: COVID-19 is known to be associated with immune-mediated vasculopathy and cause direct endothelial damage. This can compound the angioinvasive manifestation of mucormycosis, for example, the development of CRAO (central retinal artery occlusion) [45].
- *Role of zinc*: The role of zinc was investigated in vitro by comparing the growth of *Mucor* in zinc-enriched and zinc-depleted media, with the former showing growth favoring *Mucor* [56]. However, serum levels of zinc were not found to be different among patients with CAROM and COVID-19 patients without ROCM.

10.4.4 Diagnosis

The following laboratory investigations can render the confirmatory diagnosis of CAROM:

- KOH mount: This is a bedside investigation where nasal crust or tissue from necrotic areas is subjected to microscopy under 10% KOH mount [57]. The presence of septate hyphae indicates the possibility of *Aspergillus* species, whereas aseptate hyphae are pathognomic of *Mucorales* species.
- Imaging: The reasons for obtaining cross-sectional radiology are the following (Fig. 10.5):
  - To confirm the diagnosis of CAROM: Contrast-enhanced computed tomography and MRI provide complementary information in case of ROCM. The fol-

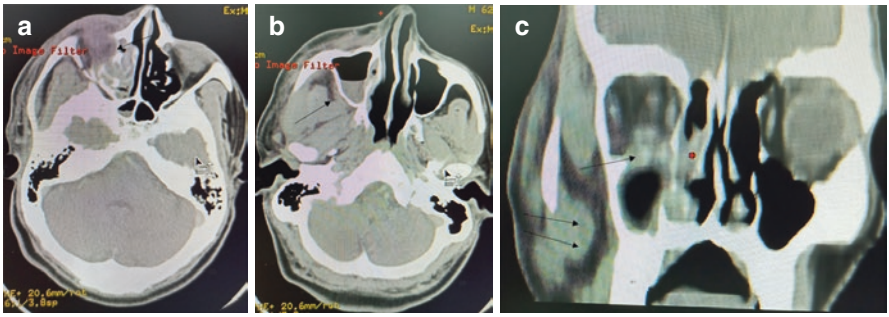

Fig. 10.5 Radiology in CAROM. (**a**) NCCT PNS revealing soft tissue in the anterior ethmoid with destruction of lamina papyracea (arrow). (**b**) Periantral fat streaking noted. (**c**) Orbital floor eroded with soft tissue tracking into the orbit and abutting inferior rectus muscle (single arrow). Accompanying inflammation seen over the premaxillary soft tissue (double arrow)

lowing radiological pointers are most often used to predict the possibility of ROCM [58]:

Presence of soft tissue in the paranasal sinuses with bone erosion.

Extrasinus spread of the disease without bone erosion signifies angio-invasiveness.

Extrasinus spread of the disease to involve the periantral fat is considered to be one of the earliest signs [59]

Fungal elements appear hypointense on T2-weighted MRI due to the presence of heavy metals. "Black turbinate" sign, where fungal elements in middle turbinate produce hypointensity of the middle turbinate, is considered one of the earliest signs of ROCM on MRI [60].

– To determine the extent of the disease:

Palatal involvement presents as bone erosion at the level of hard palate or through and through an oroantral fistula

The presence of extensive premaxillary soft tissue involvement with or without skin involvement may preclude a purely endoscopic approach.

The presence of soft tissue thickening in retroantral region and pterygomaxillary fissure necessitates an infratemporal fossa clearance.

Orbital involvement: The earliest signs of orbital invasion on radiology include soft tissue thickening at the level of the nasolacrimal duct, thickening of the medial rectus muscle, and retro-orbital fat stranding [58]. Progressive orbital involvement can be evinced by the presence of enlargement of all extraocular muscles, bone erosion at the level of lamina papyracea and inferior orbital wall, stretching and thickening of the optic nerve, presence of soft tissue at the orbital apex and superior orbital fissure, uveoscleral thickening (panophthalmitis), and tenting of the posterior pole of the globe (guitar pick sign) [58].

Intracranial involvement: Cavernous sinus involvement on MRI can be confirmed by the presence of altered signal intensity, enlargement of the

superior ophthalmic vein, and bulky cavernous sinus. Intracranial involvement can range from erosion of cribriform plate, meningeal enhancement, signs of cerebritis, to abscess formation (peripheral ring-enhancing lesion). MRI should also be reviewed carefully to rule out any vascular complications like arteritis, carotid or basilar artery narrowing, or formation of a pseudoaneurysm [58].

10.4.5 Treatment

Management of CAROM should be performed by a multidisciplinary team involving otorhinolaryngologists, infectious disease experts, intensivists, prosthodontics, plastic and reconstructive surgeons, neurosurgeons, and neurologist. The best outcomes are obtained in patients diagnosed at Talmi stages I and II and those who undergo timely debridement and initiation of antifungal therapy. Therapeutic challenges unique to CAROM are as follows:

1. Timing of debridement: Surgical intervention for ROCM is time-sensitive. A delay of 6 days in surgical debridement can double the risk of 30-day mortality [49]. However, performing an extensive paranasal sinus debridement in a COVID-19-positive set-up poses safety risk to healthcare personnel involved and adds to perioperative morbidity for the patient. Knisely et al. have compared perioperative outcomes in COVID-19-positive patients undergoing emergency surgical intervention with non-COVID-19 patients undergoing similar procedures [61]. They reported 16.7% mortality in COVID-19-positive patients compared to 1.4% in COVID-19-negative patients, along with higher ICU admission rates (36.1 vs. 16.1%). Therefore, the decision regarding expedited surgery while the patient is concomitantly COVID-19-positive needs to be individualized, taking into consideration the severity of COVID-19 illness and the extent of ROCM [45]. Gupta et al. have proposed a decision-making algorithm for CAROM, considering the severity of COVID-19 illness and ROCM [45]. It was recommended that surgery might be deferred in low-severity ROCM for about 2 weeks to reduce COVID-19-associated perioperative morbidity. In case of high-severity ROCM, debridement should be expedited. If concomitant COVID-19 severity is mild or moderate, the patient needs to be taken up for surgery under the high-risk category. However, if COVID-19 severity falls in the severe category, debridement should be deferred till the intensivist considers the patient to be hemodynamically stable to undergo the procedure.
2. The extent of surgical resection: Surgical resection should aim to remove all necrotic and devitalized tissue and eliminate the nidus of fungus. However, this is impossible to achieve completely in cavernous sinus/intracranial involvement and sometimes inappropriate in case of peripheral or early orbital involvement due to the cosmetic and functional disability consequent to orbital debridement.

   The surgical approaches available for debridement of ROCM are endoscopic and open approaches. For patients requiring palatal resection, extensive involve-

ment of premaxillary soft tissue and skin and those requiring orbital exenteration are not considered appropriate for purely endoscopic resection. Sublabial approach also offers excellent cosmetic results by avoiding facial incision in patients requiring only limited debridement.

3. Antifungal therapy: Intravenous liposomal amphotericin B is the first-line antifungal for ROCM. It should be administered at a dose of 3–6 mg/kg body weight/day. Initial high-dose treatment may limit the spread of infection, but high dosage treatment is often limited by toxicity (chills and rigors, allergic and anaphylactic reactions, dose-related nephrotoxicity). A cumulative dose of 3–5 g of amphotericin B is probably sufficient for patients with stage I/II disease wherein complete debridement is achieved. For intracranial disease, wherein complete debridement is almost never realistic, a cumulative dose of 8 g or maximum tolerable dose of amphotericin B is recommended [62].

   Oral posaconazole or isavuconazole is considered a step-down antifungal. Oral posaconazole is prescribed at a dose of 300 mg twice daily on the first day, followed by 300 mg once a day. Absorption is better when administered with a fatty meal. Serum drug level biological assays may be used to ascertain drug bioavailability.

10.5 Neuro-Otological Sequelae

1. Vertigo: Dizziness is one of the commonest neurological manifestations of COVID-19. There are anecdotal reports of vertigo persisting beyond the recovery of COVID-19 [63]. The possible causes for vertigo are vestibular neuronitis, benign paroxysmal positional vertigo, and posterior circulation stroke. Mechanisms of neuroinvasion that have been proposed include binding to ACE-2 receptors, hypercoagulopathy, hypoxia, and immune-mediated mechanisms [64, 65]. At present, there is little clarity about the outcome of COVID-19-associated dizziness. Vestibular rehabilitation measures have been shown to be of benefit [63].
2. Sensorineural hearing loss: Sudden sensorineural hearing loss (SSNHL) is defined as at least 30 dB hearing loss in three consecutive frequencies within 3 days. Post-viral SSNHL has been described with herpes virus and cytomegalovirus [66]. SSNHL in COVID-19 is now being recognized, especially following the recovery of the illness. SSNHL is frequently described with moderate and severe forms of the disease [67].

   Various theories surround the etiopathogenesis of SSNHL in COVID-19. The first hypothesis is direct damage to the epithelial cells of the organ of Corti, spiral ganglion, and the endothelial cells of stria vascularis. This is supported by the expression of ACE-2 receptors in these cells [68]. SARS-CoV-2-induced direct cochlear damage was revealed by Mustafa and colleagues, where COVID-19-infected patients were found to have a higher threshold in high frequencies and worsened threshold for transient evoked otoacoustic emission compared to normal individuals with no history of COVID-19 positivity [69]. The second plau-

sible mechanism causing inner ear damage could arise from COVID-19-induced cytokine storm [70]. Hypercoagulopathy-induced ischemic damage to the inner ear has also been proposed as mechanism for inner ear damage due to COVID-19. Treatment of SSNHL occurring in the context of COVID-19 is not different from SSNHL due to other viral etiology. First-line management consists of oral corticosteroids. Intratympanic steroid is reserved for salvage in oral steroid-unresponsive cases.

3. Tinnitus: Due to the previously described mechanisms of inner ear damage, tinnitus and balance disorders may present in patients recovering from COVID-19 [71]. In a multicentric questionnaire-based study conducted in Italy on patients who were in the 30–60 days' interval from COVID-19 diagnosis, disequilibrium was reported in 18.4% of subjects and tinnitus in 23.2%, and 7.6% reported both disequilibrium and tinnitus [71]
4. Facial palsy: SARS-CoV-2 is a neurotropic virus owing to the expression of ACE-2 receptors in the brain and cranial and peripheral nerves [72]. There is a lack of evidence currently to validate the causal role of SARS-CoV-2 in the development of facial palsy in these patients.
5. Ototoxicity: Compounds containing quinine are known to cause inner ear damage [9]. Though there have been no reports of ototoxicity following hydroxychloroquine administration for COVID-19, it is important to be aware of this adverse effect [9]. Ototoxicity following hydroxychloroquine use can present long after discontinuation of the treatment and is known to be irreversible [9].

10.6 Upper Airway Dysfunction-Related Sequelae

1. Dysphonia: Incidence of dysphonia as a primary symptom of COVID-19 ranges from 26.8 to 43.7% [20, 73]. As per the study published by Cantarella et al., 15% of these patients have persistent dysphonia beyond 1 month following the diagnosis of COVID-19 [73]. Dysphonia in mild to moderate COVID-19 was significantly associated with smoking and upper airway symptoms like rhinitis and cough [20, 73]. To the contrary, the development of dysphonia in severe COVID-19 was associated with intubation granuloma, cord palsy, and use of nebulized glucocorticoid [74]. Underlying pathophysiology includes vocal cord strain from cough and rhinitis, recurrent laryngeal nerve damage from the virus, recurrent laryngeal nerve compression due to the endotracheal tube, and the "corditis" theory [74]. Direct virus-induced vocal cord inflammation or corditis is supported by the expression of ACE-2 receptors on vocal cord epithelium and the presence of isolated dysphonia in patients with no other upper airway inflammatory symptoms and no history of steroid use or endotracheal intubation [15, 74].
2. Tracheal stenosis: There have been anecdotal reports of tracheal stenosis developing secondary to prolonged intubation for severe COVID-19 [8]. This typically manifests as progressive shortness of breath and noisy breathing following a trial of extubation. Diagnosis can be confirmed on fiber-optic bronchoscopy,

X-ray soft tissue, and non-contrast computed tomography of the neck and chest. Bilateral cord palsy should be considered in the differential diagnosis. Management depends on the length of stenosis, the extent of airway compromise, and proximity to the subglottis. Tracheostomy is performed as an emergent measure to secure the airway. Subsequent treatment ranges from repeated endoscopic dilatation to resection of the stenosed segment and end to end anastomosis.

10.7 Sequelae Related to Upper Aerodigestive Tract-Lymphoreticular System

Kawasaki-like syndrome following COVID-19 infection has been described predominantly in the pediatric population and rarely in adults [75]. ENT manifestations include multiple cervical lymphadenopathies (most commonly jugulodigastric node) and oral mucosal lesions (strawberry tongue). Awareness among ENT practitioners is necessary since ENT manifestations often precede multisystem organ involvement [75].

10.8 Post-COVID-19 Thyroiditis

Subacute thyroiditis (SAT), also known as de Quervain's thyroiditis, has been described in association with post-COVID-19 sequelae. In a systematic review published by Rehman and colleagues, SAT symptoms appeared after an average of 25.2 ± 10.1 days from the diagnosis of COVID-19 [76]. SAT is a self-limiting condition progressing through three phases: hyperthyroid, hypothyroid, and euthyroid. It is associated with a rise in inflammatory serum markers (ESR and CRP). Management consists of nonsteroidal anti-inflammatory drugs and corticosteroids. Since SAT has previously been linked to viral illnesses like mumps, measles, rubella, coxsackievirus, and adenovirus, SAT in association with COVID-19 is also likely due to direct virus-induced damage or related to virus-induced inflammatory response [76, 77].

10.9 Take-Home Points

1. Post-COVID-19 chemosensory dysfunction can be persistent in 7.2% of individuals.
2. Thorough ENT evaluation, the patient-reported structured questionnaires, paranasal sinus and brain imaging, and objective testing using quantitative olfactory testing complete the work-up for post-COVID-19 chemosensory dysfunction.
3. Evidence-based treatment recommendations are most robust for early initiation of olfactory training.
4. Topical steroid spray may be recommended along with olfactory training. Currently, there is a paucity of evidence favoring oral steroid administration.

5. Development of ROCM in the background of COVID-19 (CAROM) can be linked to uncontrolled hyperglycemia, steroid administration, COVID-19-induced iron overload state, immunosuppression arising from IL-6 antagonist use, and decrease in phagocyte activity and hypercoagulability.
6. In patients with a high index of suspicion toward CAROM, the diagnosis can be rendered following 10% KOH examination of the tissue and imaging of the paranasal sinus and brain.
7. Treatment of CAROM should include timely initiation of amphotericin B and timely surgical debridement. Oral posaconazole is used as a step-down antifungal.
8. Involvement of orbit, cavernous sinus, and intracranial extension ported a poor outcome with high mortality rates.

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